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A STUDY OF BLOOD BY CHEMICAL ANALYSIS AND BY DIGITAL COMPUTER: A COMPARATIVE EVALUATION

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Abstract

Blood chemistry has been a subject of intense study that has produced an enormous amount of data relating to the entire physiologic system. Recent developments in programming techniques have made possible the simulation of the blood chemical system. In order to validate such a model, a set of rigorous experiments was designed to be independently performed on blood in the laboratory and on the blood model.

Sodium bicarbonate addition to blood is known to alter a wide variety of chemical constituents in such a manner as to facilitate reliable measurements in the laboratory. Independent additions of this chemical to blood both in the model and in the laboratory produced well correlated results.

The effect of hypothermia on blood hydrogen ion concentration was also examined as a function of the validity of the model. Laboratory and model results of this experiment not only agreed well, but also directed attention to the importance of constancy of ambient gas concentrations when these measurements are made, a point frequently overlooked in clinical medicine.

The blood model is of primary advantage in correlating the chemical structure of blood, in quantitating clinically significant chemical alterations, and in directing attention to areas of clinical significance and investigative interest.

A STUDY OF BLOOD BY CHEMICAL ANALYSIS AND BY DIGITAL COMPUTER: A COMPARATIVE EVALUATION*

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INTRODUCTION

In the evolution of man, organization of form took place in such a manner that blood became a highly-specialized, complex, functionally delineated part of the human structure. Of its many important characteristics, blood is clinically interesting particularly because it comes into intimate contact with every other tissue in the body and hence reflects the chemical composition and chemical function of the tissues and organs. Blood chemistry has, therefore, been a subject of intense study that has produced an enormous amount of data relating to the entire physiologic system. However, although most of these data are presented in tabular and nomographic form in current handbooks, computational techniques have not been available to rigorously interrelate the data in a manner similar

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to the complex interrelations of a biologic subsystem. Recent developments of chemical programming on high-speed computers have made such simulation of great complexity possible. In fact, not only is it possible to show the detailed interrelations of the pertinent, important chemical reactions of a subsystem, but it is possible to examine the system under widely varying or even dynamic boundary conditions.

It is proposed in this paper to examine the validity of such a mathematical model of blood by comparing the model to the time-honored methods of chemical laboratory analysis. If a mathematical model of a complex biochemical system such as blood is validly functional, it should be possible to perform identical chemical experiments with the model and in the laboratory and to obtain identical results.

METHOD

As a collaborative effort, the disciplines of research and clinical medicine, mathematics, physical chemistry, and computer technology were combined. Under this organization, a series of experiments upon blood were conducted independently with the mathematical blood model and in the surgical and chemical laboratories. The conditions of the experiments, decided upon in advance, consisted of arbitrary physical and chemical stress as applied to normal blood.

No attempt will be made in this paper to present the chemical and mathematical bases of the blood model, because they have been described in detail elsewhere.[3,4,5,8] Briefly, the chemical states of the blood in the model are determined by the thermodynamic relations that pertain as the result of reactions occurring within the blood and as the result of its contact with its environments, the pulmonary alveoli and the tissue cells. By minimizing the

free energy of the system subject to constraints relating to conservation of mass and neutrality of electrical charge, the chemical steady states characteristic of different internal and external conditions can be determined. Because of the complexity of the model and the requirements for accurate fast solutions, experiments with it are conducted on a large, high-speed, digital computer.

In the laboratory, most experiments were carried out in siliconized, sterile, clean glassware at temperatures and gas concentrations specified by the experimental design. Hematocrit was determined by micro and macro methods according to standard centrifugation techniques, and in each case corrected for trapped plasma. Sodium and potassium determinations were made in a Beckman flame photometer, Model DU. Chloride was determined according to the method of Kingsley and Dowdell.[6] pH and pCO_2 were determined by the method of Astrup.[2]

THE EXPERIMENTS

External Respiration: The model includes the important chemical aspects of the human external respiratory system (gas exchange and blood chemistry at the alveolar surface). The ability of the model to reproduce accurately the chemical changes of blood as it is transformed from the venous state to the arterial state at the lungs is itself a strenuous test of the model, since a large quantity of data exists on this subject. These data from many laboratory determinations have been appropriately averaged to establish norms and minimize random laboratory error. As seen in Table I, the model values for normal blood and those from the Handbook of Biological Data agree within -0.84 mean per cent difference, S.E. $\pm$ 0.94.

Chemical Stress: Various chemical stresses were applied to blood in its model form and in its real form in the laboratory. These stresses consisted of the separate

TABLE 1

COMPARISON OF COMPUTER OUTPUTS WITH STANDARD BIOLOGICAL DATA

INPUTS	Computer (Moles/Vol Produced)	Handbook of Biological Data (Moles/Vol Existing)
	Alveolar Gas	
O_2	0.1314	0.1315
CO_2	0.0526	0.0526
N_2	0.754	0.754
H_2O	0.0610	0.0611
	Plasma	
O_2	6.65×10^{-5}	6.34×10^{-5}
CO_2	6.87×10^{-5}	6.96×10^{-4}
N_2	2.13×10^{-4}	2.16×10^{-8}
H^+	2.06×10^{-8}	2.10×10^{-7}
OH^-	3.07×10^{-7}	3.57×10^{-2}
Cl^-	5.70×10^{-2}	5.70×10^{-2}
Na^+	7.64×10^{-2}	7.64×10^{-2}
K^+	2.31×10^{-3}	2.31×10^{-3}
H_2O	2.83×10	2.87×10
HCO_3^-	1.38×10^{-2}	1.37×10^{-2}
H_2CO_3	9.77×10^{-7}	Not reported
$CO_3^=$	1.95×10^{-5}	Not reported
Ca^{++}	2.85×10^{-3}	2.86×10^{-3}
Mg^{++}	9.35×10^{-4}	9.35×10^{-4}
	Red Cells	
O_2	7.03×10^{-5}	6.43×10^{-5}
CO_2	4.44×10^{-4}	4.73×10^{-4}
N_2	2.28×10^{-4}	2.20×10^{-4}
H^+	2.14×10^{-8}	2.09×10^{-8}
OH^-	1.23×10^{-7}	1.41×10^{-7}
Cl^-	2.29×10^{-2}	2.40×10^{-2}
Na^+	8.36×10^{-3}	8.37×10^{-3}
K^+	4.27×10^{-2}	4.27×10^{-2}
H_2O	1.83×10	1.80×10
HCO_3^-	6.40×10^{-3}	5.98×10^{-3}
H_2CO_3	6.32×10^{-7}	Not reported
$CO_3^=$	5.63×10^{-6}	Not reported
Ca^{++}	4.10×10^{-4}	4.5×10^{-4}
Mg^{++}	2.29×10^{-3}	2.29×10^{-3}

Mean % difference = - 0.84
S. E. = ± 0.94

additions of lactic acid to simulate metabolic acidosis, varying amounts of carbon dioxide to simulate respiratory acidosis and alkalosis, water to give overhydration, and hypertonic saline to simulate salt concentration. Experiments with addition alkalosis (sodium bicarbonate) were selected for presentation here because this stress was found to produce the greatest alterations in blood chemistry. 44.6 milliequivalents of sodium bicarbonate in 50 ml. water were added to one liter of blood. pCO_2 and pO_2 were maintained constant, and the reaction was allowed to go to completion at $37^{0}C$. Table II compares the results of this stress as measured by the mathematical model and by laboratory analysis. A discrepancy between the measured and computed results was noted in the initial experiments because of the sodium contained in the heparin used as an anticoagulant. Later experiments, in which minute amounts of heparin were used, gave excellent correlation between measured and computed data. Nevertheless, all experiments are included in Table II.

Physical Stress: Current cardiovascular, cancer, and neurological surgical techniques occasionally require that the temperature of the patient be markedly reduced. Since the original use of hypothermia as an adjunct to surgery, a controversy has existed concerning the effect of hypothermia on blood. When the blood model was subjected to reduced temperatures, the hydrogen ion concentration of blood cells and blood plasma increased. Published observations of the characteristics of blood during hypothermia are divided as to the occurrence of an alkalosis or an acidosis.[1,7] Blood was then subjected to hypothermia in the experimental laboratory, and the model results were confirmed. The wide difference in the acid-base status of blood during hypothermia is frequently only a product of the conditions under which it is measured, and the buffering capacity of the blood. The effects of such changing

TABLE 2

COMPARISON OF LABORATORY RESULTS WITH MODEL PREDICTIONS

FOR BLOOD CHANGES IN ADDITION ALKALOSIS

BLOOD CONSTITUENTS	Before Na HCO_3	After Na HCO_3	
	Normal Values	Lab. (10 Experiments)	Computer
Hct	45 vol %	37.2	36.9
Plasma Na^+	139 mEq/L	188	178
Plasma K^+	4.2 mEq/L	4.5	4.52
Plasma Cl^-	103 mEq/L	102.7	97.5
Plasma H^+	3.8×10^{-8} M/L	1.58×10^{-8}	1.24×10^{-8}
Osmolality	290 mOsm/L	370	380

conditions on the pH is illustrated in Fig. 1 where the data of Rosenthal[7] were obtained with varying pCO_2 whereas the laboratory and computer results maintained constant pCO_2 but varied in the buffer capacity of the blood. Figure 2 shows the close agreement between oxygen dissociation curves (for blood at pH 7.4 and at three different temperatures) obtained by the model and those presented in the Handbook of Respiration.

Physicochemical Stress: In several of the experiments on chemical stress, data from the model indicated that certain previously unrecognized physicochemical reactions took place. One of the most prominent of these appeared when water or saline was added to the blood. In the model, when water acting as a solvent for any physiological solute is added to blood in the presence of physiological gas mixtures, an acidosis of mild degree occurs. The model indicated this effect to be due to the solubility of carbon dioxide in the added water. The carbon dioxide hydrates to carbonic acid, which upon ionization provides hydrogen ions and thereby depresses the pH of blood.

This same experiment was performed in the laboratory, both on blood residing outside of the body and that within an anesthetized dog. In both cases, when saline was infused, the pH decreased when carbon dioxide was absorbed from the gas phase. The pH decrease is illustrated in Fig. 3.

DISCUSSION

A comparison is made regarding two means of evaluating blood, both under normal conditions and under conditions of varying types of stress. The two methods of evaluation are seen to be comparable.

In the first experiment, that of normal external respiration, a model is constructed that equilibrates venous blood with lung gases and produces arterial blood

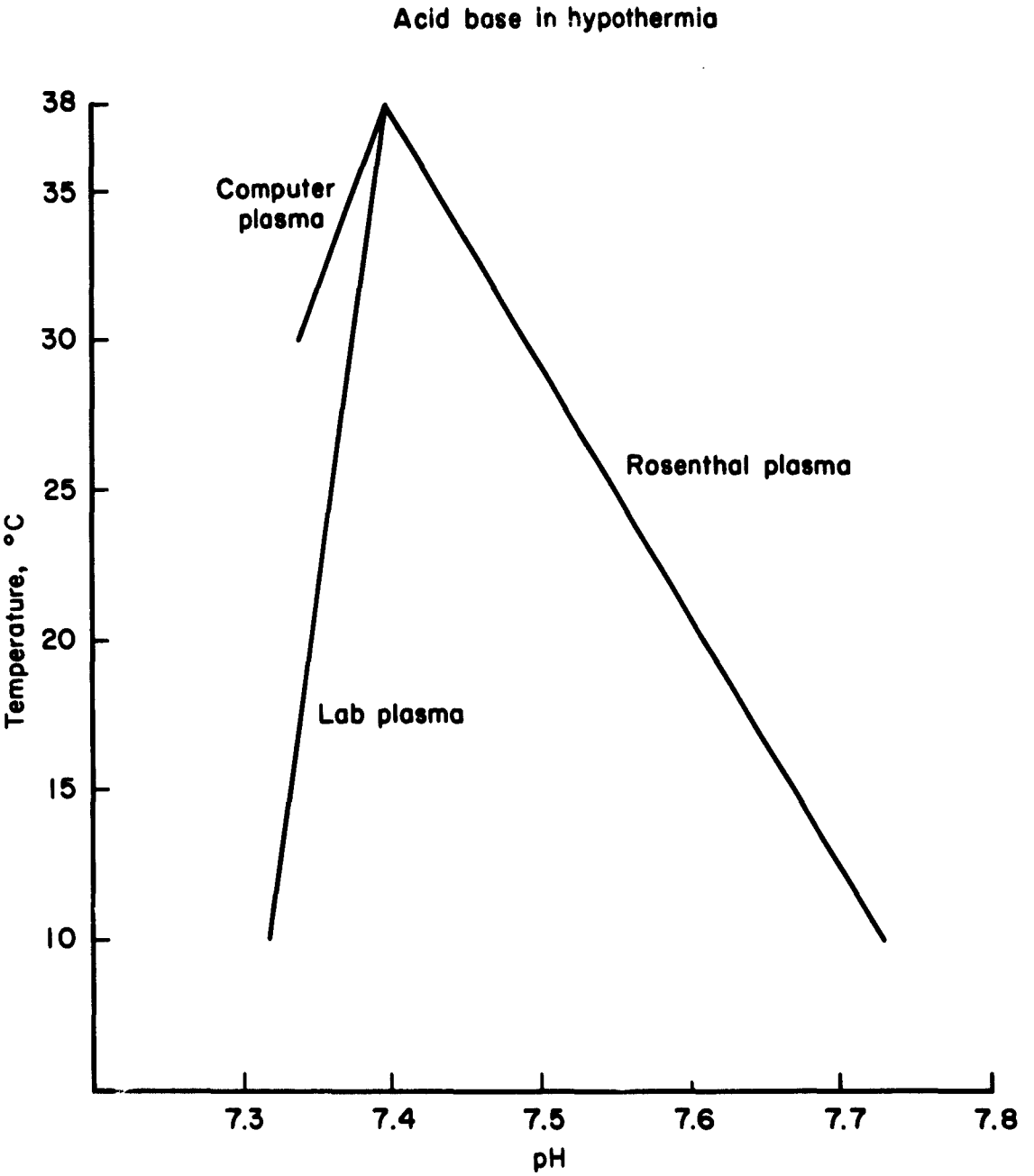

Fig. 1 – Variations of plasma pH with temperature under different conditions of measurement (See text for definition of conditions.)

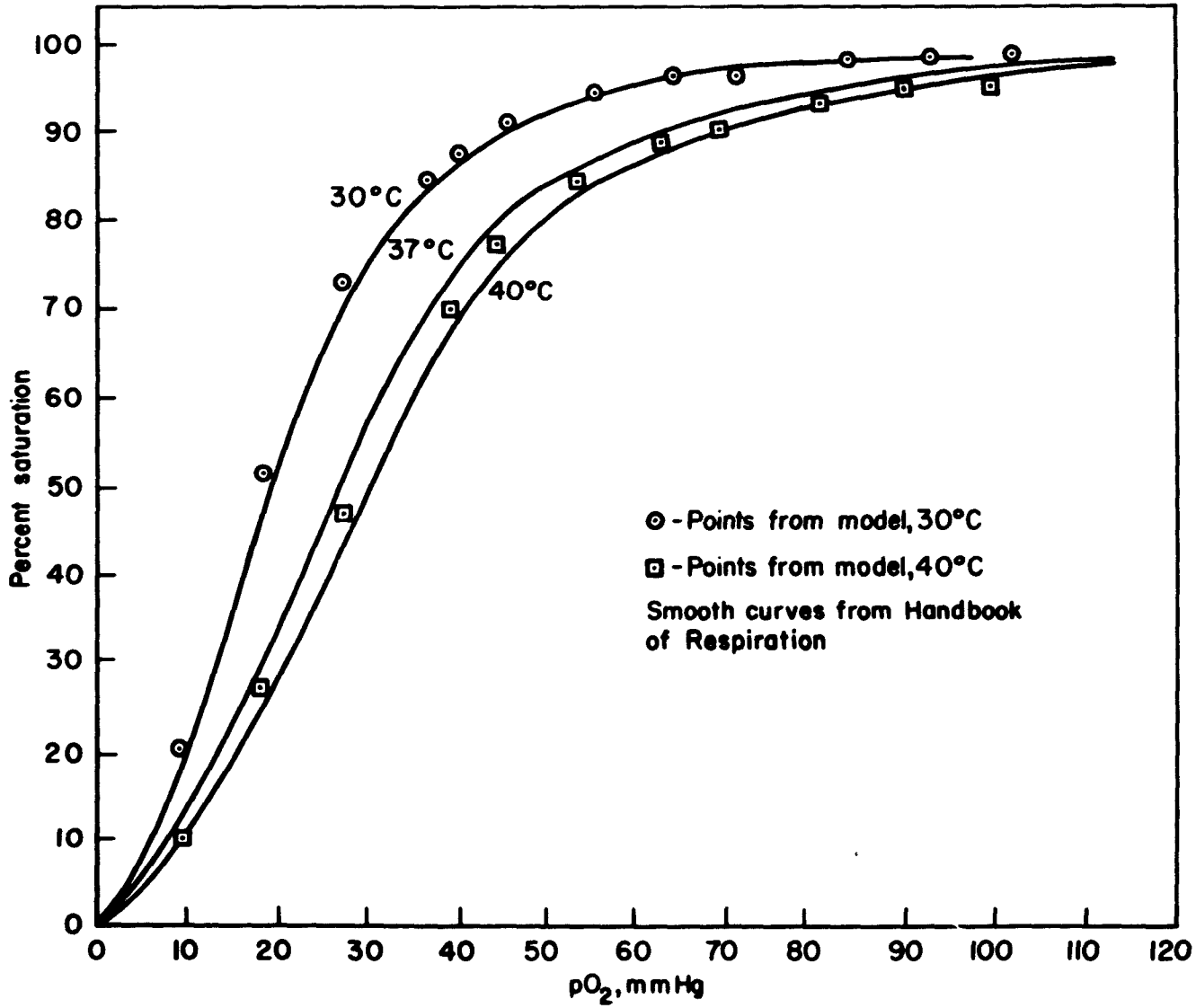

Fig. 2 — Comparison of oxygen dissociation curves obtained from computer model and from handbook

SALINE ACIDOSIS

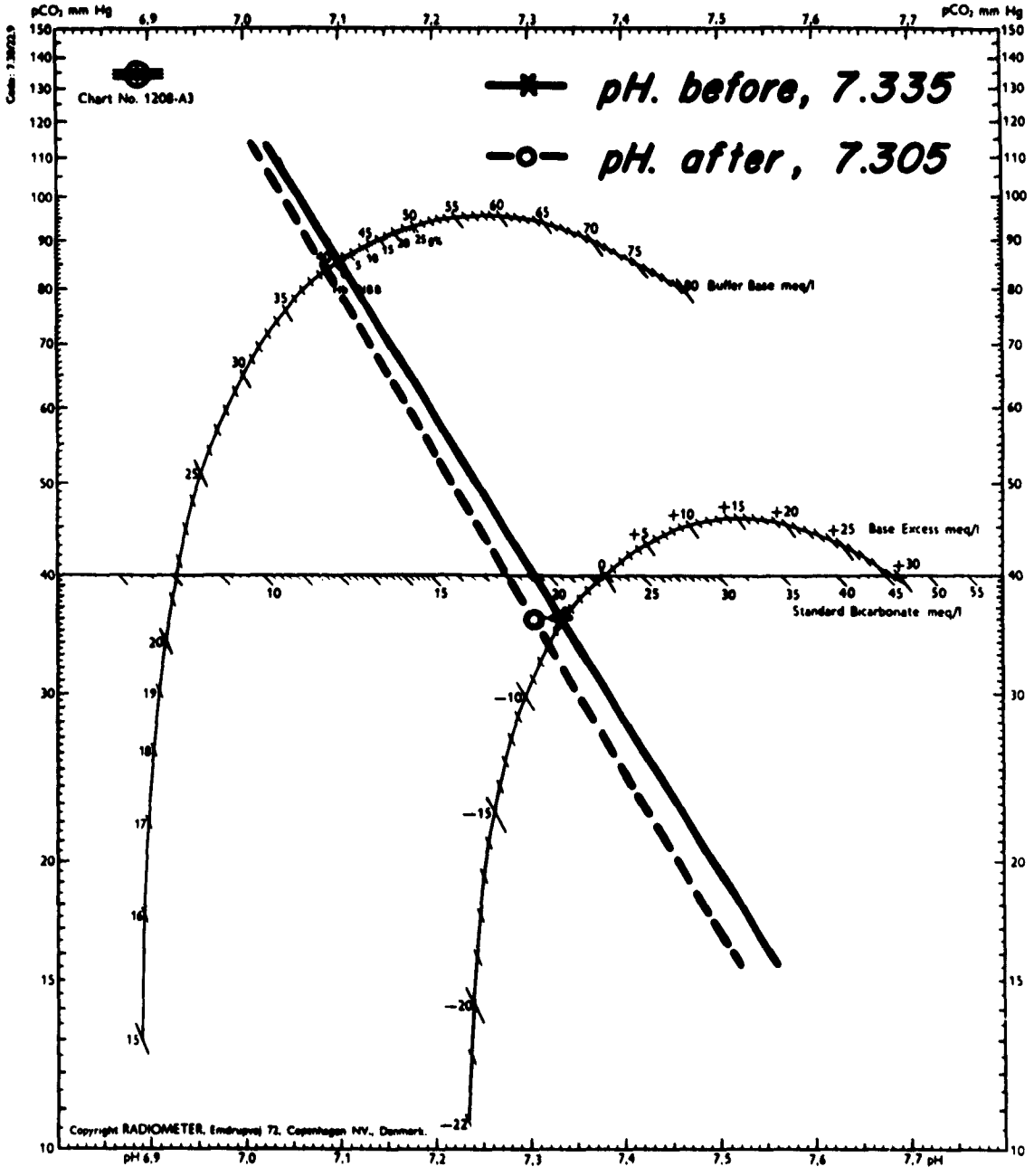

Fig.3 — Astrup nomogram showing saline acidosis in a dog.

from this equilibration. The results of this experiment are actually of better accuracy than any single laboratory test. It is therefore immediately obvious that a valuable tool for the study of human respiratory factors is available.

The set of experiments concerned with application of chemical stress is relatively easy to perform with the model, but presents certain difficulties within the laboratory. Repetitive laboratory experiments are necessary to provide a mean of inherent population differences and to eliminate random laboratory error. The blood from the human donor must be immediately fresh, to present the accumulation of the products of metabolism. The anticoagulents necessary in laboratory experiments inevitably alter blood chemistry to some degree. Despite these difficulties, a reasonable correlation of the effects of chemical stress between computer and laboratory is presented.

In the example of physical stress, immediately useful clinical information was provided. The subject of pH changes in hypothermia has been largely misunderstood, due to a lack of definition of the conditions under which the pH should be measured.[1] The experiments on the model and in the laboratory direct attention to the fact that if pCO_2 is held constant while hypothermia is induced, the pH of blood will not change appreciably.

Stress to the organism has previously been considered largely in the light of either chemical stress or physical stress. The blood model will frequently resolve these two categories into a physicochemical stress, as it did in the example of "saline acidosis." While the extent of this particular acidosis is not clinically significant, the ability of a model to predict a previously unrecognized physical-chemical event in everyday patient treatment is of profound significance.

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